#6
7/11/01
M.J.

PATENT
#Y2-0121-UNI
Case #J3515(C)

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to:

"Assistant Commissioner for Patents
Washington, D.C. 20231"

on June 20, 2001

MATTHEW BOXER
Reg. No. 28,495
Attorney for Applicant(s)

06/20/01
Date of Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Clarkson et al.

Serial No.: 09/764,735

Filed: January 17, 2001

For: ANTIMICROBIAL COMPOSITIONS

Edgewater, New Jersey 07020
June 20, 2001

SUBMISSION OF PRIORITY DOCUMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Pursuant to rule 55(b) of the Rules of Practice in Patent Cases, Applicant(s) is/are submitting herewith a certified copy of the United Kingdom Application No. 0001129.6 filed January 18, 2000, upon which the claim for priority under 35 U.S.C. § 119 was made in the United States.

It is respectfully requested that the priority document be made part of the file history.

Respectfully submitted,

Matthew Boxer
Reg. No. 28,495
Attorney for Applicant(s)

MB/mt
(201) 840-2963

PATENTS • DESIGNS • COPYRIGHT • TRADE MARKS
The Patent Office

INVESTOR IN PEOPLE

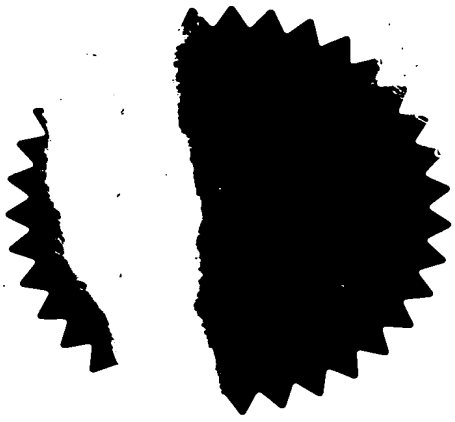
The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed R. Mahoney

Dated 11 January 2001

Patents Form 1/77

THE PATENT OFFICE
F
18 JAN 2000
LONDON

The Patent Office

19JAN00 E506234-3 D02898
P01/7700 0.00-0001129.6

The Patent Office
Cardiff Road
Newport
Gwent NP10 8QQ

Patents Act 1977
(Rule 16)

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

1.	Your reference	J3515(C)/PMK
2.	Patent application number *(The Patent Office will fill in this part)*	18 JAN 2000 **0001129.6**
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	**UNILEVER PLC** **UNILEVER HOUSE, BLACKFRIARS** **LONDON, EC4P 4BQ**
	Patents ADP number *(if you know it)*	
	If the applicant is a corporate body, give the country/state of its incorporation	**UNITED KINGDOM** 1628001
4.	Title of the invention	**ANTI-MICROBIAL AEROSOL COMPOSITIONS**
5.	Name of your agent *(if you have one)*	**PEARCE, Timothy**
	"Address for Service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	**PATENT DEPARTMENT, UNILEVER PLC** **COLWORTH HOUSE, SHARNBROOK** **BEDFORD, MK44 1LQ** 7667579001
	Patents ADP number *(if you know it)*	

6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing *(day/month/year)*

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *See note (d))*	**YES**

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	22
Claim(s)	3
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how may against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature(s) Date: **18/01/00**

Sandra Jane EDWARDS, Authorised Signatory

12. Name and daytime telephone number of person to contact in the United Kingdom — **Petra Kimber, Tel 01234 222893**

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.
b) Write your answers in capital letters using black ink or you may type them.
c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.
e) Once you have filled in the form you must remember to sign and date it.
f) For details of the fee and ways to pay please contact the Patent Office.

Anti-microbial Aerosol Compositions

Field of Invention

This invention relates to the field of anti-microbial aerosol compositions and to methods of reducing microbial numbers. In particular, this invention is concerned with reducing microbial numbers upon the surface of the human body and thereby reducing body odour. The compositions and methods involved utilise propellant-driven solutions of transition metal chelators as anti-microbial agents. When used on the human body, the compositions and methods of the invention are of greatest benefit when used on the most malodorous areas of the human body, for example the underarm areas or feet.

Background

Anti-microbial agents may function by a variety of means. When used upon the human body, such agents may significantly reduce microbial numbers either by reducing perspiration or by directly effecting the micro-organisms on the surface of the body as represented herein by skin. It is with this latter class of agents, often called deodorant agents, that this invention is largely concerned.

Most deodorant agents reduce the number of viable micro-organisms on the surface of the skin. It is well known that sweat is usually odourless until it has been degraded by the skin microflora. Typical deodorants include ethanol and triclosan (2',4,4'-trichloro,2-hydroxy-diphenyl ether) which is a well known anti-microbial agent. However, the deodorising effect obtained with such deodorants wears off with the passage of time and the microflora progressively recover their numbers.

There is, therefore, a continuing requirement for effective, long lasting deodorant compositions for the market. The problem to be solved is not simply reducing microbial numbers on the body surface; equally important is maintaining low microbial numbers (particularly low bacterial numbers) on the body surface (particularly in the most malodorous areas, eg. the axillae).

Certain transition metal chelators have previously been incorporated into deodorant compositions. US 4,356,190 (Personal Products Co.) discloses the use of selected aminopolycarboxylic acid compounds for inhibiting the formation of short chain fatty acids by Corynebacterium on the skin surface. For topical application, alkanolamine salts are stated to be preferred. Especially preferred salts are stated to be di- and trialkanolamine salts such as triethanolamine, diethanolamine, and triisopropanolamine salts. It is also stated that solvents, including organic solvents, compatible with the system in which the chelator is incorporated may be employed; however, products comprising solutions of chelators in such solvents are not disclosed.

WO 97/02010 (Procter and Gamble Co.) discloses the use of chelators selected from the succinic acid, glutaric acid, and phosphonic acid classes as bactericidal compounds.

WO 97/44006 (Ciba Speciality Chemicals Holding, Inc.) claims the use of nitrogen-containing complexing agents for the anti-microbial treatment of the skin and of textile fibre materials. Particular complexing agents mentioned include those formed from neutralising EDDS with ethanolamine or laurylamine. Deodorant compositions comprising chelators and 60% aqueous ethanol are also disclosed; however, aerosol compositions are not contemplated.

WO 97/01360 (Concat Ltd.) claims a method of inhibiting bacterial growth using particular substituted polyaza compounds that show affinity for first transition series elements. It is stated that compatible salts may be formed by neutralisation with inorganic or organic bases, including primary, secondary and tertiary amines, notably ethanolamine, diethanolamine, morpholine, glucamine, N,N-dimethylglucamine, and N-methylglucamine.

Other patents indicate that transition metal chelators can improve the efficacy of particular known anti-microbials. WO 98/12399 (Public Health Research Institute of the City of New York) discloses improved performance of lanthionine-containing bacteriocins in compositions also comprising a transition metal chelator. WO 97/09974 (Laboratoire Medix) discloses compositions comprising chlorhexidine and a chelator. EP 0019670 B1 (Glyco Chemicals, Inc.) discloses anti-microbial compositions comprising a condensation product of 5,5-dimethyl hydantoin and formaldehyde in combination with a water-soluble chelating agent selected from ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA) or the alkali metal salts thereof. US 4,199,602 (Economics Laboratory, Inc.) discloses the potentiation of anti-microbial nitroalkanes by aminocarboxylic-type chelating agents. US 5,688,516 (University of Texas System et al) discloses compositions comprising non-glycopeptide anti-microbials (other than vancomycin) in combination with a selection of components, including a chelating agent. WO 99/10017 (University of Texas System et al) discloses a method for controlling the growth of micro-organisms using a chelating agent and an anti-microbial agent. GB 1,420,946 (Beecham Group Ltd.) discloses that the activity of selected phenolic anti-microbials can be vastly increased by certain chelating agents, in particular the disodium salt of EDTA.

Summary of the Invention

This invention is concerned with the formulation of stable, prolonged activity, anti-microbial aerosol compositions comprising a transition metal chelator and/or a salt thereof.

It has now been discovered that by using transition metal chelators and/or salts thereof in a carrier fluid comprising both an organic solvent and water, anti-microbial compositions can be formulated at elevated pressure with hydrophobic aerosol propellants also present. In addition, such products can deliver prolonged anti-microbial activity. The prolonged anti-microbial activity often manifests itself as a long-lasting deodorancy benefit, for example lasting a day. The stability of the compositions of the invention is a result of good compatibility between the components - this leads to benefits in terms of performance, stability, and aesthetics. Preferred compositions of the invention are homogeneous solutions even when fully formulated, that is to say even with the usually highly hydrophobic volatile propellant present. Such solution compositions have advantages with respect to many of the problems associated with alternative suspension compositions; for example, reducing or avoiding problems with valve blocking, settling and caking of the suspended solids, and uneven application to the surface requiring treatment can all be reduced.

Thus, according to a first aspect of the present invention, there is provided an anti-microbial aerosol composition comprising a volatile propellant, a carrier fluid, and a transition metal chelator and/or salt thereof, characterised in that the carrier fluid comprises both an organic solvent and water. In preferred embodiments, such anti-microbial compositions function as deodorant compositions.

According to a second aspect of the present invention, there is provided a method of controlling microbial numbers, said method comprising the application to a substrate of an anti-microbial aerosol composition comprising a volatile propellant, a carrier fluid, and a transition metal chelator or salt thereof, characterised in that the carrier fluid comprises both an organic solvent and water. An application of this aspect of the invention is the control of microbial numbers on the surface of the human body, for example skin which is representative of an external surface populated by microrganisms which generate odour from body secretions and the resulting control of malodour of the human body, using said anti-microbial aerosol compositions.

According to a third aspect of the present invention, there is provided a method for the manufacture an anti-microbial aerosol composition, said method comprising the formation of a solution of a transition metal chelator and/or salt thereof in a carrier fluid comprising an organic solvent and water, followed by the dilution and pressurisation of the solution by a liquefied volatile propellant.

Detailed Description

The novel anti-microbial aerosol compositions of the invention perform unexpectedly well in terms of anti-microbial efficacy and maintenance of low malodour, particularly when applied to the human body. Without wishing to be bound by theory, it is hypothesised that after reduction of microbial numbers by other co-applied agents and/or by some external treatment like washing, the chelator effectively inhibits the up-take of essential transition metal ion nutrients by the remaining microbes, thereby minimising their re-growth.

When preferred compositions according to the invention are applied to surfaces the volatile propellant evaporates, leaving the chelator and/or salt thereof in the form of a solution in the carrier fluid upon the surface being treated. This can lead to significant benefits, both in terms of performance and aesthetics, for example lack of powdery deposits. Preferred compositions comprise a solution of the chelator and/or salt thereof in the carrier fluid. Preferably, such solutions have an absorbance, relative to the carrier fluid, of less than 0.2, especially less than 0.1 (for a 1 cm pathlength at 600 nm) measured using a Pharmacia Biotech Ultrospec 200 Spectrophotometer or similar instrument. Preferred compositions are homogeneous solutions even when fully formulated. It is preferred that such full composition solutions also meet the absorbance criteria set out above: less than 0.2, especially less than 0.1, measured at 600 nm.

Preferred chelators and/or salts thereof for use in the current invention comprises an anionic chelator for a transition metal and an organic cation. The use of a carrier fluid comprising an organic solvent and water together with a transition metal chelator salt having an organic cation gives good compatibility between components. In preferred compositions the formation of a solution of chelator salt in the carrier fluid occurs. In addition, the benefit of good compatibility with the (usually highly hydrophobic) volatile propellant is attained.

Particularly preferred organic cations comprise protonated or quaternised amines, particularly those comprising a C_1-C_{10} terminal hydrocarbyl group, wherein a hydrocarbyl group is a radical comprising solely carbon and hydrogen atoms. Such

relatively hydrophobic cations can enable the ready solubilisation of the relatively hydrophilic chelator salt anions in the carrier fluid. They also enable excellent compatibility with other relatively hydrophobic components present in the composition.

Preferred protonated or quaternised amine cations of the chelator salts are of formula $R^1R^2R^3R^4N^{(+)}$, wherein R^1 is H or CH_3; R^2, R^3, and R^4 are each independently H or an aliphatic or aromatic substituent containing 0 to 3 hydroxyl groups, optionally interrupted and/or substituted by functional groups such as ether, amine, ester, or amide; with the provisos that at least one of R^2, R^3, or R^4 comprises a C_1-C_{10} terminal hydrocarbyl group, optionally R^2 and R^3 together forming a ring as the terminal hydrocarbyl group, and that R^2, R^3, and R^4 are not all $CH_2CH(OH)CH_3$ groups.

Of the aforementioned preferred transition metal chelators of formula $R^1R^2R^3R^4N^{(+)}$, particularly preferred are transition metal chelators having cations characterised in that at least one of R^2, R^3, or R^4 comprises an H atom directly attached to an N atom or an O atom. The presence of an H atom directly attached to an O atom (ie. a hydroxyl group) in at least one of R^2, R^3, or R^4 is especially preferred, up to the aforementioned limit of 3 hydroxyl groups per N-substituent.

Other particularly preferred transition metal chelator salts have cations comprising N-substituents (R^1, R^2, R^3, and R^4, according to the formula) that collectively contain a total

of 0 to 3 hydroxyl groups, preferably 0 to 2 hydroxyl groups.

In many desirable chelator salts, each N-substituent (R^1, R^2, R^3, and R^4, according to the formula) contains not more than one hydroxyl group.

Especially preferred chelator salts are salts of aliphatic amines, characterised in that, in said amines, the ratio of the total number of H atoms directly attached to an N atom or an O atom to the total number of carbon atoms is not greater than 3:4.

The compositions of the invention may be applied to the surface requiring treatment by any means. Whilst direct application is likely to be the most common method for most product uses, pre-application onto a carrier matrix like paper, fabric, or sponge and application by contacting said carrier matrix with the surface, is also a possibility.

Chelators

Some preferences for the chelators of the compositions of the invention are described hereinbefore.

Preferred anti-microbial aerosol compositions of the invention comprise transition metal chelators and/or salts thereof having affinity for iron (III), in particular chelators having high affinity for iron (III); that is to say, a binding constant for iron (III) of greater than 10^{10}, or, for optimum performance, greater than 10^{26}. The 'iron (III) binding constant' referred to above is the absolute stability constant for the chelator-iron (III) complex.

Such values are independent of pH and consider only the most anionic, fully deprotonated form of the chelator. Measurements can be made potentiometrically, and in a number of other ways. Full details of suitable methods can be found in "Determination and Use of Stability Constants", A. E. Martell and R. J. Motekaitis (VCH, New York, 1989). Tables of such values may be found in numerous sources, for example "Critical Stability Constants", R. M. Smith and A. E. Martell (Plenum Pub. Corp., 1977).

Preferred compositions comprise chelators which are able to significantly inhibit the growth of a relevant micro-organism when present, in a medium containing said micro-organism, at a concentration of 3×10^{-5} $mol.dm^{-3}$ or less. Inhibition is considered significant when growth of the relevant micro-organism on a supporting medium can be reduced by at least 30%, preferably by at least 45%. When the substrate to be treated is human skin, a relevant micro-organism is *Staphlococcus epidermidis* and chelators capable of achieving significant inhibition include diethylenetriaminepentaacetic acid (DTPA) and triethylenetetraaminehexaacetic acid (TTHA), but exclude ethylenediaminetetraacetic acid (EDTA) and trans-1,2-diaminocyclohexane-N,N,N',N'-tetraacetic acid (CDTA).

The chelators used in the present invention preferably have acid forms with at least two ionisable acid groups. The acid groups are preferably carboxylic and/or phosphonic, but may be sulphonic or phosphinic, or any mixture of these groups.

Preferred chelators with phosphonic acid groups are, in the acid form, diethylenetriaminepenta(methylphosphonic) acid (DTPMP), ethanehydroxydiphosphonic acid (EHDP), ethylenediaminetetra(methylenephosphonic acid) (EDTMP), and

hexamethylenediaminetetra(methylenephosphonic acid) (HMDTMP).

Particularly suitable chelators with acid forms having carboxylic acid groups are polycarboxylate compounds, in particular aminopolycarboxylate compounds. The acid forms of the aminopolycarboxylate compounds include EDTA, CDTA, and ethylenediaminedisuccinic acid (EDDS). More preferred aminopolycarboxylate chelators have the acid forms DTPA, TTHA, and N,N'-ethylenebis[2-(2-hydroxyphenyl)glycine] (EDDHA).

The chelators preferably have only moderate molecular weight, by which it is meant that the chelators, in their acid forms, have a molecular weight of less than 1000, more preferably 200 to 800, and most preferably 290 to 580, and in their salt form have a molecular weight of less than 2000, more preferably 300 to 1400, and most preferably 500 to 1000.

The chelator is preferably incorporated into the composition at a level of 0.01% to 10%, more preferably at a level of 0.05% to 5%, and most preferably at a level 0.3% to 3% by weight of the non-volatile components of the composition. Mixtures of chelators and their salts may also be used.

Herein, non-volatile components are those having a boiling point greater than 20°C at atmospheric pressure.

Partial salts of chelator acids possessing more than one acidic group may be employed; such salts retain one or more non-ionised acid groups. Other salts that can sometimes be used to advantage are ones where the cations are in part protonated or quaternised amines and in part some other cation, for example an alkali metal cation, in particular a

sodium ion. Whilst such mixed ionisation states are acceptable, for solutions comprising an organic solvent in the carrier fluid, it is preferred that the chelator salts have at least 40% of their available acid groups in the form of salts with protonated or quaternised amines.

Preferred chelator salts have protonated amines as cations. The following further preferences apply to the amines used:

It is preferred that the chelator salt is of an amine of relatively low odour. This is of potential benefit during manufacture and during selection and use of compositions comprising such amine salts. Related to this point is the preference for the amine to have relatively low volatility: a boiling point of 130°C or greater at atmospheric pressure being preferred.

It is preferred that the chelator salt is of an amine that is a liquid, at room temperature and atmospheric pressure. This can be of advantage with regard to formulation and processing.

It is preferred that the chelator salt is of an aliphatic amine, rather than an aromatic amine.

Preferred chelator salts are salts of isopropanolamine, 2-amino-2-ethyl-1,3-propanediol, 2-(N,N-dimethylamino)-2-methyl-1-propanol and N,N-dimethylaminoethanol. Particularly preferred chelator salts are salts of 2-amino-2-methyl-1-propanol (AMP), diisopropanolamine, 2-aminobutan-1-ol, and cyclohexylamine.

Carrier Fluid

The carrier fluid comprises an organic solvent and water. It is most convenient to employ a water-miscible organic solvent. Preferably the weight ratio of organic solvent to water is greater than 50:50, more preferably greater than

90:10. In particularly preferred compositions the weight ratio of organic solvent to water is between 95:5 and 99:1. Compositions with relatively low levels of water can be of value in products applied to the human body. When such compositions contain relatively high levels of water, they can sometimes cause an undesirable wet sensation on application. Relatively low water level compositions can also be of benefit with regard to container choice: such compositions enable metal containers to be used with less risk of corrosion. A further benefit of compositions having relatively low water levels is their compatibility with additional hydrophobic components, for example perfume components (see "Perfumery: practice and principles", R.R.Calkin and S.Jellinek, [Wiley, 1994, p171]).

To aid compatibility between the organic solvent and the chelator and/or salt thereof, it is preferred that the organic solvent is relatively polar, having a c.logP of less than 2, especially −2 to 1, and in particular −0.5 to 0.5. c.logP is the calculated logarithm to the base 10 of the octanol:water partition coefficient; a method for calculating such values may be found in "Computer-assisted computation of partition coefficients from molecular structures using fragment constants", J.Chou and P.Jurs, J. Chem. Inf. Comput. Sci., 19, 172 (1979). In addition, preferred organic solvents have a melting point of less than 10°C, preferably less than 5°C; this can benefit both low temperature storage stability and ease of manufacture. Preferred organic solvents are aliphatic alcohols (monohydric or polyhydric, preferably having 2 to 8 carbon atoms) and polyglycol ethers, preferably oligoglycol ethers having only 2 to 5 repeat units. Examples include dipropylene glycol, glycerol (c.logP −1.538) propylene glycol (c.logP −1.06), butylene glycol (c.logP −0.728),

ethanol (c.logP 0.235), propanol (c.logP 0.294), isopropanol (c.logP −0.074), and industrial methylated spirits. The most preferred organic solvents are aliphatic alcohols, in particular those having 2 to 3 carbon atoms, especially ethanol and isopropanol. Mixtures of organic solvents may also be used.

Volatile Propellant

The aerosol compositions of the invention preferably comprise from 30 to 99 parts by weight, and particularly 35 to 87 parts by weight of propellant.

The propellant may be selected from liquefied hydrocarbons or halogenated hydrocarbon gases (particularly fluorinated hydrocarbons such as 1,1-difluoroethane and/or 1-trifluoro-2-fluoroethane) that have a boiling point of below 10°C and especially those with a boiling point below 0°C. It is preferred to employ non-chlorinated volatile propellants. It is especially preferred to employ liquefied hydrocarbon gases, and especially C_3 to C_6 hydrocarbons, including propane, isopropane, butane, isobutane, pentane and isopentane and mixtures of two or more thereof. Preferred propellants are isobutane, isobutane/isopropane, isobutane/propane and mixtures of isopropane, isobutane and butane.

Other propellants that can be contemplated include alkyl ethers, such as dimethyl ether or compressed non-reactive gasses such air, nitrogen or carbon dioxide.

Additional Components

An additional component that can sometimes augment the efficacy of a composition is an additional anti-microbial agent. Most of the classes of agents commonly used in the art can be incorporated into compositions of the invention. Levels of incorporation are preferably from 0.01% to 3%, more preferably from 0.03% to 0.5% by weight of the non-volatile components of the composition. (Non-volatile meaning having a boiling point greater than 20°C.) Preferred compositions of the invention comprise an additional anti-microbial agent having a minimum inhibitory concentration (MIC) of 1 $mg.ml^{-1}$ or less, particularly 200 $\mu g.ml^{-1}$ or less, and especially 100 $\mu g.ml^{-1}$ or less. The MIC of an anti-microbial agent is the minimum concentration of the agent required to significantly inhibit microbial growth. Inhibition is considered "significant" if an 80% or greater reduction in the growth of an inoculum of a relevant micro-organism is observed, relative to a control medium without an anti-microbial agent, over a period of 16 to 24 hours at 37°C. The "relevant micro-organism" used for testing should be representative of those associated with the substrate to be treated. When the substrate to be treated is human skin, a relevant micro-organism is Staphylococcus epidermidis. Other relevant micro-organisms include Coryneform spp., Salmonella spp., Escherichia Coli, and Pseudomonas spp., in particular P. aeruginosa. Details of suitable methods for determining MICs can be found in "Antimicrobial Agents and Susceptibility Testing", C.Thornsberry, (in "Manual of Clinical Microbiology", 5th Edition, Ed. A. Balows et al, American Society for Microbiology, Washington D.C., 1991). A particularly suitable method is the Macrobroth Dilution Method as described in Chapter 110 of above publication (pp.

1101-1111) by D. F. Sahm and J. A. Washington II. MICs of anti-microbials suitable for inclusion in the compositions of the invention are triclosan: 0.01-10 $\mu g.ml^{-1}$ (J.Regos et al., Dermatologica (1979), 158: 72-79) and farnesol: ca. 25 $\mu g.ml^{-1}$ (K. Sawano, T. Sato, and R. Hattori, Proceedings of the 17th IFSCC International Conference, Yokahama (1992) p.210-232). By contrast ethanol and similar alkanols have MICs of greater than 1 $mg.ml^{-1}$. Preferred anti-microbials are bactericides, in particular organic bactericides, for example quaternary ammonium compounds, like cetyltrimethylammonium salts; chlorhexidine and salts thereof; and diglycerol monocaprate, diglycerol monolaurate, glycerol monolaurate, and similar materials, as described in "Deodorant Ingredients", S.A.Makin and M.R.Lowry, in "Antiperspirants and Deodorants", Ed. K. Laden (1999, Marcel Dekker, New York). More preferred anti-microbials for use in the compositions of the invention are polyhexamethylene biguanide salts (also known as polyaminopropyl biguanide salts), an example being Cosmocil CQ™ available from Zeneca PLC, preferably used at up to 1% and more preferably at 0.03% to 0.3% by weight; 2',4,4'-trichloro,2-hydroxy-diphenyl ether (triclosan), preferably used at up to 1% by weight of the composition and more preferably at 0.05-0.3%; and 3,7,11-trimethyldodeca-2,6,10-trienol (farnesol), preferably used at up to 1% by weight of the composition and more preferably at up to 0.5%.

Inorganic anti-microbial agents may also be used in the compositions of the invention. Such materials often also function as anti-perspirant agents. Examples are often selected from astringent active salts, including, in particular, aluminium, zirconium and mixed

aluminium/zirconium salts, including both inorganic salts, salts with organic anions and complexes. Preferred astringent salts include aluminium, zirconium and aluminium/zirconium halides and halohydrate salts, such as chlorohydrates. When included, preferred levels of incorporation are from 0.5% to 60%, particularly from 5% to 30% or 40% and especially from 5% or 10% to 30% or 35% by weight of the composition. Especially preferred aluminium halohydrate salts, known as activated aluminium chlorohydrates, are described in EP 6,739 (Unilever PLC and NV). Zirconium aluminium chlorohydrate actives are also preferred materials, as are the so-called ZAG (zirconium-aluminium-glycine) complexes, for example those disclosed in US 3,792,068 (Procter and Gamble Co.). Zinc phenol sulphonate may also be used, preferably at up to 3% by weight of the composition.

It should be noted that incorporation of amphoteric or cationic anti-microbial agents makes it particularly important to use the compositions of the present invention. This is particularly true of organic anti-microbial agents, of cationic anti-microbial agents, and especially true of organic polycationic anti-microbial agents. In this context, "polycationic" means possessing more than one positive charge, although the importance of the use of chelator salts in accord with the present invention is even greater in the presence of organic polycationic anti-microbial agents that possess more than five positive charges per molecule.

Certain sensory modifiers are further desirable components in the compositions of the invention. Emollients, humectants, volatile oils and non-volatile oils are all suitable classes of sensory modifiers. Examples of such materials include cyclomethicone, dimethicone, dimethiconol,

isopropyl myristate, isopropyl palmitate, C12-C15 alcohol benzoate, PPG-3 myristyl ether, octyl dodecanol, C7-C14 isoparaffins, di-isopropyl adipate, isosorbide laurate, PPG-14 butyl ether, glycerol, hydrogenated polyisobutene, polydecene, phenyl trimethicone, dioctyl adipate, and hexamethyl disiloxane.

Fragrance is also a desirable additional component in the compositions of the invention. Suitable materials include conventional perfumes, such as perfume oils and also include so-called deo-perfumes, as described in EP 545,556 and other publications. Levels of incorporation are preferably up to 4% by weight, particularly from 0.1% to 2% by weight, and especially from 0.7% to 1.7% by weight.

It should be noted that certain components of compositions perform more than one function. Such components are particularly preferred additional ingredients, their use often saving both money and formulation space. Examples of such components include ethanol and isopropyl myristate.

Further additional components that may also be included are colourants, preservatives, for example C_1-C_3 alkyl parabens, and anticlogging agents, at conventional concentrations.

The aerosol composition is usually filled into an aerosol canister that is capable of withstanding pressures generated by the formulation, employing conventional filling apparatus and conditions. The canister can conveniently be a metal canister commercially available fitted with a dip tube, valve and spray nozzle through which the formulation is dispensed.

Methods of Manufacture

The compositions of the invention are generally manufactured by forming of a solution of a transition metal chelator and/or salt thereof in the carrier fluid and then diluting and pressurising it with a liquefied volatile propellant. Details of the preparation of a specific anti-microbial aerosol composition according to the invention are given as Example 1.

Examples

(Note that "letter" codes refer to Comparative Examples.)

Example 1: Preparation of a DTPA-AMP Aerosol Deodorant

0.52 g of DTPA was added as a powder to 65.91 g of 96% (w/w) ethanol. To this mixture was added (dropwise, with stirring) 0.38 g of AMP. The resulting mixture was stirred, with gentle heating (50°C) for 30 minutes. 0.34 g of isopropyl myristate was added to the resulting solution and mixed in. The resulting mixture was sealed into a conventional aluminium deodorant can, having valve access, and 36.16 g of liquified propellant (CAP 40, *ex* Calor) was introduced into the can from a propellant 'transfer can', *via* the valve, using a polyethylene transfer device. Finally, the can was fitted with a suitable actuator to enable effective spray application of the product.

Deodorancy Test 1

An anti-microbial composition according to the current invention (Example 1) and a control composition (Comparative Example A – lacking the chelator-amine salt, see Table 1 for compositions) were prepared according to the method

described. The deodorancy performances of the two compositions were tested according to the following protocol. The results, presented in Table 1, illustrate the deodorancy benefit obtained from using an example prepared according to the invention. This benefit is a direct result of the anti-microbial performance of the composition.

Deodorancy protocol

The panel employed comprised 50 individuals who had been instructed to use control ethanolic deodorant products during the week prior to the test. At the start of the test, panellists were washed with unfragranced soap and test product (1.20g) applied to one axilla and control product applied (1.20g) to the other. (Product application was randomised to take into account any left/right bias). Panellists were instructed not to consume spicy food or alcohol, and not to wash under their own axillae, during the duration of the test. At least three expert assessors determined the intensity of axillary odour at 5 hours and 24 hours after application, scoring the intensity on a scale of 1-5. After each 24 hour assessment, the panellists were re-washed, and products re-applied, as above. The procedure was repeated 4 times. At the end of the test the data were analysed using standard statistical techniques.

Table 1: DTPA-AMP salt vs. Control

Component		Example A	Example 1
DTPA[1] (as free acid)		0	0.5
AMP[2]		0	0.37
Isopropyl myristate[3]		0.33	0.33
Water		2.59	2.56
Ethanol		62.08	61.24
CAP40[4]		35	35
Mean malodour intensity[5]	5 hour	2.2	1.86
	24 hour	2.36	2.01

All components are expressed as weight per cent of the total components added.

1. diethylenetriaminepentaacetic acid.
2. 2-amino-2-methyl-1-propanol, used to form the amine salt of the chelator.
3. Emollient.
4. Propellant, proprietary mix of butane, isobutane and propane, ex. Calor.
5. The malodour differences between the compositions were significant at the 99% level, after both 5 hours and 24 hours. (Minimum differences required for significance at the 95% and 99% confidence levels were:
   after 5 hours: 0.14 for 95% level; 0.19 for 99% level;
   after 24 hours: 0.17 for 95% level; 0.22 for 99% level).

Deodorancy Test 2

The deodorancy protocol described above was also used to test the performance of Examples B and 2 (see Table 2). These Examples were prepared in a similar manner to Examples A and 1, with the modification that a fragrance material was added to the compositions shortly before introduction into the conventional aluminium deodorant cans.

Table 2: Fragranced DTPA-AMP salt vs. Fragranced Control

Component		Example B	Example 2
DTPA (as free acid)		0	0.5
AMP		0	0.37
Isopropyl myristate		0.33	0.33
Water		2.53	2.49
Ethanol		60.64	59.81
CAP40		35	35
Fragrance		1.5	1.5
Mean malodour intensity	5 hour	1.34	1.13
	24 hour	2.07	1.71

All components are expressed as weight per cent of the total components added.

The malodour differences between the compositions were significant at the 99% level, after both 5 hours and 24 hours. (Minimum differences required for significance at the 95% and 99% confidence levels were:

after 5 hours: 0.10 for 95% level; 0.13 for 99% level;
after 24 hours: 0.10 for 95% level; 0.13 for 99% level).

Examples 3 to 6: Further Aerosol Compositions

Neutral DTPA salt compositions were prepared according to Table 3. 76 mmol.kg^{-1} solutions of the indicated chelator-

amine salts in 96:4 (w/w) ethanol/water, also containing perfume (1.5% w/w) and isopropyl myristate (0.33% w/w), were pressurised to about 2.7 bar with a proprietary mixture of propane, isobutane, and N-butane (CAP40, 22:24:54, ex Calor). The resulting pressurised systems, contained liquified propellant:base in the weight ratio 35:65, DTPA being present at about 13 $mmol.kg^{-1}$, based on the total weight of all components present, including the propellants. All of these products were homogeneous solutions.

Table 3: DPTA salts in 96% Ethanol and CAP40

Component	Example			
	3	4	5	6
DTPA (as free acid)	0.5	0.5	0.5	0.5
Diisopropanolamine	0.42	0	0	0
AMP	0	0.37	0	0
2-amino-2-butanol	0	0	0.31	0
Cyclohexylamine	0	0	0	0.42
Isopropyl myristate	0.33	0.33	0.33	0.33
Water	2.55	2.56	2.55	2.55
Ethanol	61.20	61.25	61.31	61.20
CAP40	35	35	35	35

All components are expressed as weight per cent of the total components added.

Claims

1. An anti-microbial aerosol composition comprising a volatile propellant, a carrier fluid, and a transition metal chelator and/or salt thereof, characterised in that the carrier fluid comprises both an organic solvent and water.

2. An anti-microbial composition according to claim 1, that is also a deodorant composition for use on the human body.

3. An anti-microbial composition according to claim 1 or 2, characterised in that the chelator and/or salt thereof is fully soluble in the carrier fluid at the relative concentrations present in the composition.

4. An anti-microbial composition according to any of the preceding claims, characterised in that the chelator and/or salt thereof comprises an anionic chelator for a transition metal and an organic cation.

5. An anti-microbial composition according to claim 4, characterised in that the organic cation of the chelator salt is a protonated or quaternised amines comprising a C_1-C_{10} terminal hydrocarbyl group.

6. An anti-microbial composition according to any preceding claim, wherein the transition metal chelator or salt thereof salt has affinity for iron (III).

7. An anti-microbial composition according to claim 6, wherein the transition metal chelator or salt thereof

salt has a binding coefficient for iron (III) of greater than 10^{26}.

8. An anti-microbial composition according to any preceding claim, wherein the transition metal chelator or salt thereof is a polyaminocarboxylic acid or salt thereof.

9. An anti-microbial composition according to claim 8, wherein the polyaminocarboxylic acid or salt thereof is diethylenetriaminepentaacetic acid or a salt thereof.

10. An anti-microbial composition according to any preceding claim, characterised in that the weight ratio of organic solvent to water is greater than 50:50.

11. An anti-microbial composition according to claim 10, characterised in that the weight ratio of organic solvent to water is between 95:5 and 99:1.

12. An anti-microbial composition according to any preceding claim, wherein the chelator or salt thereof is present at a concentration of 0.01% to 10% by weight of the total weight of non-volatile components present.

13. An anti-microbial aerosol composition according to any preceding claim, characterised in that the organic solvent has a c.logP of less than 2.

14. An anti-microbial composition according to claim 13, characterised in that the organic solvent comprises ethanol or isopropanol.

15. An anti-microbial aerosol composition according claim 13 or 14, comprising a non-chlorinated volatile propellant.

16. An anti-microbial composition according to any preceding claim, also comprising an additional anti-microbial agent.

17. An anti-microbial composition according to claim 16, characterised in that the additional anti-microbial agent is a cationic bactericide.

18. An anti-microbial composition according to any preceding claim, also comprising a fragrance material at up to 4%.

19. A method of controlling microbial numbers, said method comprising the application to a substrate of an anti-microbial aerosol composition according to any preceding claim.

20. A cosmetic method of inhibiting the generation of human body odour comprising the topical application to body skin of a composition according any one of claims 1 to 18.

21. A method for the manufacture an anti-microbial aerosol composition, said method comprising the formation of a solution of a transition metal chelator and/or salt thereof in a carrier fluid comprising an organic solvent and water, followed by the dilution and pressurisation of the solution by a liquefied volatile propellant.